REMARKS

Claims 29-38 remain in this case, claim 37 having been restricted out pursuant to a prior restriction requirement.

Claims 28, 29, 31, 32 and 34 have been rejected as obvious over Zukowski (WO 97/40755) in view of the patents to Kropf (4,760,849) and Eury (5,605,696) while claims 30, 33, 35, 36 and 38 were rejected as obvious over Zukowski (WO 97/40755) in view of the patents to Kropf (4,760,849) and Eury (5,605,696) and Ragheb (5,873,904).

The Cited Art

The **Zukowski** publication (WO 97/40755) is directed to a device used to repair defective venous valves. The embodiment of figures 15-18 is made by spirally winding strips of porous expanded PTFE about a mandrel, winding reinforcing wires about the mandrel and heating the mandrel to soften the PTFE so that the wires becomes embedded in and adhere to the PTFE. The structure may be provided with an outer covering of another layer of PTFE adhered to the first layer. The device is positioned externally around the vein at the site of the defective valve. The device provides an external, constricting force to the vein to partially flatten the vein to an oval shape to help restore proper valve operation. Figure 18 shows a helical support which "is deformed by compression to assume the transversely elliptical cross-section." (Page 9, lines 23-35.) .

Kropf U.S. Patent No. 4,760,849 discloses a ladder type stent.

Eury U.S. Patent Number 5,605,696 discloses adding a therapeutic drug as a component of a polymeric material. The drug-containing polymeric material can be laminated to one or both of the surfaces of a stent. The stent is typically stainless steel or some other metal. (Column 3, lines 24-35; column 5, lines 37-53.) Eury discloses a "laundry list" of different drugs that can be used with the Eury invention.

> "The selected therapeutic drug can, for example, be anticoagulant antiplatelet or antithrombin agents such as heparin, D-phe-pro-arg-chloromethylketone (synthetic antithrombin), dipyridamole, hirudin, recombinant hirudin, thrombin inhibitor (available from Biogen), or c7E3 (an antiplatelet drug from Centocore); cytostatic or antiproliferative agents such as angiopeptin (a somatostatin analogue from Ibsen), angiotensin converting enzyme inhibitors such as Captopril (available from Squibb), Cilazapril (available from Hoffman-LaRoche), or Lisinopril (available from Merk); calcium channel blockers (such as Nifedipine), colchicine, fibroblast growth factor (FGF) antagonists, fish oil (omega 3-fatty acid), low molecular weight heparin

(available from Wyeth, and Glycomed), histamine antagonists, Lovastatin (an inhibitor of HMG-CoA reductase, a cholesterol lowering drug from Merk), methotrexate, monoclonal antibodies (such as to PDGF receptors), nitroprusside, phosphodiesterase inhibitors, prostacyclin and prostacyclin analogues, prostaglandin inhibitor (available from Glaxo), Seramin (a PDGF antagonist), serotonin blockers, steroids, thioprotease inhibitors, and triazolopyrimidine (a PDGF antagonist). Other therapeutic drugs which may be appropriate include alphainterferon and genetically engineered epithelial cells, for example." Column 3, line 60-column 4, line 16.

Ragheb U.S. Patent No. 5,873,904 discloses a medical device 10 including a structure 12, typically a vascular stent 12, composed of an elastic/non-elastic, biodegradable/non-biodegradable base material 14, such as stainless steel, nitinol, polymers, etc. Stent 12 is shown to have several layers of materials coated thereon. At least one layer 18 of a bioactive material is on the surface of stent 12. An outer porous layer 20 surrounds layer 18 to provide controlled release of the bioactive material. A porous/non-porous layer 16 may be used between the bioactive layer 18 and stent 12. A second bioactive layer 22 may be used between porous layer 20 and bioactive layer 18; if so, an inner porous layer 24 may be used between the bioactive layers 18, 22.

The Cited Art Distinguished

Independent **claim 28** has been amended to emphasize that the stent graft is an endoluminal (that is, used within a lumen) stent graft. Support for this amendment can be found at page 1, line 12-page 3, line 20 and figures 7A-7C. Claim 28 is allowable over the cited art for a number of reasons. The Zukowski publication does not disclose an endoluminal stent graft because it is used outside, not inside, a lumen to provide an external, constricting force to the vein to partially flatten the vein to an oval shape to help restore proper valve operation. There is no evidence to support its use as an endoluminal stent graft. There is nothing in the art that would support modifying the structure of Zukowski to transform it into an endoluminal stent graft. Even assuming, for sake of discussion, that it would have been obvious to combine the cited art as suggested in the Office Action, the result would, applicant submits, be at most an external, constricting vascular structure as disclosed in Zukowski incorporating the ladder-type stent structure of Kropf and a therapeutic drug layer of Eury; such a structure would not be the invention of claim 28.

Independent claim 28 has also been written to recite "an NO generator located entirely within the porous tubular graft material" and has been amended to emphasize that the NO generator is "dispensable through the graft material." It has been found that nitric oxide (NO) is useful to reduce restenosis. See **Exhibit A**, John B. Cooke MD PhD, *Nitric Oxide and Restenosis, A Report For Vascular Architects*, Sept. 16, 2002. [Exhibits A-F can be found with the prior amendment filed on 27 January 2003.] However, the testing discussed at **Exhibit B,** Junghan Yoon, et al, *Local Delivery of Nitric Oxide from an Eluting Stent to Inhibit Neointimal Thickening in a Porcine Coronary Injury Model, Yonsei Med J*, Vol. 43, No. 2, pp.242-251, 2002, discloses that coating stents with an NO generator incorporated into a polymer was not an effective method for delivery of NO. "However, this sodium nitroprusside-eluting stent failed to reduce chronic neointima thickening in the porcine coronary stent injury model." Exhibit B, page 250.

In contrast, applicants have found through experimentation that a stent graft made according to claim 28 (**Exhibit C**, aSpire® covered stent Product Literature) released NO at a therapeutically effective level for over 60 days. It is believed that this extended-length release period is due to the containment of the NO generator within the porous tubular graft material. See **Exhibit D** (declaration of Kirti Kamdar describing the experiment) and **Exhibits E and F** (plots of NO vs. time for the experiment).

Applicant is not taking the position that the use of an NO generator per se is new. Rather, the art fails to recognize that there would be an advantage in using an NO generator within a porous tubular graft material as presently claimed. The patent to Eury discloses a laundry list of 30 or so therapeutic agents and provides absolutely no guidance that would cause one of ordinary skill in the art to select nitroprusside, an NO generator, over the multitude of other agents listed. Rather, the evidence of record, discussed above, teaches away from coating stents with an NO generator. Further, there is nothing in the art that teaches or suggests using "an NO generator located entirely within the porous tubular graft material and dispensable through the graft material."

Accordingly, claim 28 is allowable over the cited art.

The dependant claims are directed to specific novel subfeatures of the invention and are allowable for that reason as well as by depending from novel parent claims.

CONCLUSION

In light of the above remarks and the amendments to the claims, applicants submit that the application is in condition for allowance and action to that end is urged. If the Examiner believes a telephone conference would aid the prosecution of this case in any way, please call the undersigned at (650) 712-0340.

Respectfully submitted,
HAYNES BEFFEL & WOLFELD LLP

Date: 21 May 2003 By: _____
James F. Hann, Reg. No. 29,719

HAYNES BEFFEL & WOLFELD LLP
P.O. Box 366
Half Moon Bay, CA 94019
Telephone: 650-712-0340/Facsimile: 650-712-0263

Exhibits: [Exhibits A-F can be found with the prior amendment filed on 27 January 2003.]

A: John B. Cooke MD PhD, *Nitric Oxide and Restenosis, A Report For Vascular Architects*, Sept. 16, 2002.

B: Junghan Yoon, et al, *Local Delivery of Nitric Oxide from an Eluting Stent to Inhibit Neointimal Thickening in a Porcine Coronary Injury Model,* Yonsei Med J, Vol. 43, No. 2, pp.242-251, 2002.

C: aSpire® covered stent Product Literature

D: Declaration of Kirti Kamdar

E: Elution Data (the results of Groups 1 and 2 plotted separately)

F: T 1/2 (single plots for Group 1 and 2 plus a best-fit curve)